cosolvent, wherein said inhaler has an internal surface and all or part of said internal surface is a material selected from the group consisting of stainless steel and anodized aluminum.

The inventors have surprisingly found that the presently claimed MDIs unexpectedly reduce the chemical degradation of the active ingredient contained in the MDI. The cited reference contains no disclosure or suggestion of such a MDI. Moreover, this reference contains no teaching which would suggest the improved chemical stability of the active ingredient contained in the presently claimed MDI. Accordingly, this reference cannot affect the patentability of the present claims.

The rejections of Claims 11, 12, 14, and 17-19 under 35 U.S.C. §102(e) and Claims 13, 15, 16, and 20-44 under 35 U.S.C. § 103(a) in view of U.S. Patent No. 6,143,277 (Ashurst et al '277) is respectfully traversed. Ashurst et al '277 discloses certain MDIs in which all or part of the internal surface is coated with one or more fluorocarbon polymers, optionally in combination with one or more non-fluorocarbon polymers, for dispensing an inhalation drug formulation comprising salmeterol.

However, as clearly stated in column 1, lines 19-26 and lines 29-33, the drug, salmeterol, is present in the inhalation formulation as a finely divided powder ***suspended*** in a liquefied propellant (*see also*, the Examples at cols. 7 to 10). Ashurst et al '277 discloses that the technical problem in this kind of suspension formulation is that:

> Some aerosol drugs tend to adhere to the inner surfaces, i.e., walls of the can, valves, and caps, of the MDI. This can lead to the patient getting significantly less than the prescribed amount of drug upon each activation of the MDI.
>
> *See*, col. 1, lines 51-54.

The solution to this problem proposed in Ashurst et al '277 is to use a MDI in which the interior surface is coated with a fluorocarbon polymer (*see*, col. 1, lines 59-63).

Thus, Ashurst et al '277 is only concerned with a problem which is specific to suspensions and does not disclose any MDI which contain a solution of an active agent.

In sharp contrast, the present claims explicitly recite that the MDI contains "a ***solution*** comprising an active ingredient." As explained above, the inventors have discovered that the presently claimed MDI unexpectedly afford a dramatic improvement in the chemical stability of the active ingredient in the solution contained in the MDI.

As pointed out during the above-mentioned interview with the Examiner, the distinction between Ashurst et al '277 and the presently claimed MDI is discussed in the present specification. Ashurst et al '277 is a continuation-in-part ("CIP") of U.S. patent application serial no. 08/583,332, which was a CIP of U.S. patent application serial no. 08/422,370, which was filed as International Application No. PCT/US96/05005, which was published as WO 96/32150. In addition, U.S. Patent No. 6,131,566 (Ashurst et al '566, cited by the Examiner) is a CIP of U.S. patent application serial no. 08/584,860, which was a CIP of U.S. patent application serial no. 08/422,371, which was a continuation of International Application No. PCT/US96/05002, which was published as WO 96/32099.

WO 96/32150 and WO 96/32099, along with some other published PCT applications, are discussed in the present specification:

> WO 96/32099, WO 96/32150, WO 96/32151 and WO 96/32345 disclose metered dose inhalers for the administration of different active ingredients ***in suspension*** in the propellant, wherein the internal surfaces of the inhaler are partially or completely coated with one or more fluorocarbon polymers optionally in combination with one or more non-fluorocarbon polymers.

> Said applications do not however address the technical problem of ***the chemical stability of the active ingredient but they rather concern a different problem, namely that of the adhesion of micronized particles of the suspended active ingredient to the internal surfaces of the inhaler, such as the can walls, valves and sealings.***
>
> page 3, lines 15-28, emphasis added.

In sharp contrast, the problem solved by the present invention is quite distinct from that of Ashurst et al '277. As explained on page 3, lines 4-6, of the present specification, "the widespread use of [HFA solution] formulations is limited by their chemical instability, causing the formation of degradation products."

In other words, the present invention relates to a pressurized metered dose inhaler which contains a ***solution*** comprising an active ingredient, wherein said inhaler has an internal surface and all or part of said internal surface is a material selected from the group consisting of stainless steel and anodized aluminum. As explained in the present specification, the inventors have found that:

> the chemical stability problems of active ingredients in solution in HFA propellants can be eliminated by storing and delivering said composition employing metered-dose inhalers having part or all of their internal metallic surfaces consisting of stainless steel, anodized aluminum or lined with an inert organic coating.
>
> The preferred material for the aerosol cans is anodized aluminum.
>
> *See*, page 4, line 26, to page 5, line 5.
>
> * * *
>
> The inhalers according to the invention effectively prevent the chemical degradation of the active ingredient.
>
> See, page 5, lines 26-28.

* * *

> Active ingredients which may be used in the aerosol compositions to be dispensed with the inhalers of the invention are any ingredient which can be administered by inhalation and which meets ***problems of chemical stability in solution in HFA propellants*** giving rise to a decomposition when stored in conventional materials cans and in particular in aluminum cans.
>
> See, page 6, line 28, to page 7, line 7.

There is no disclosure of the problem of chemical stability Ashurst et al '277. At most, one would look to the disclosure of Ashurst et al '277 to address the specific disclosed problem with ***suspensions***. Since the present claims are directed toward MDI which contain a ***solution*** of the active ingredient, one of skill in the art would not look to Ashurst et al '277 to address the problem of chemical stability encountered with such solutions.

For all of these reasons, the present claims are patentable over Ashurst et al '277, and the rejection should be withdrawn.

Lastly, Applicants wish to point out the existence of certain errors in Table 3 on page 19, of the specification as filed. Specifically, the numbers given for the amounts of citric acid in the first two rows of data are incorrect. The amount in the first row should read 0.01 % w/w, rather than 0.6 % w/w and the amount in the second row should read 0.04 % w/w, rather than 0.3 % w/w. The data given in the third row was actually obtained using 0.08 % w/w of citric acid, which is considered to be essentially the same as the amount listed (0.07 % w/w), and this data is considered to be correct.

Applicants expressly state on the record that the data in the first two rows of Table 3, on page 19 of the specification, do not represent the best mode of carrying out the invention as contemplated by the inventors at the time the application was filed. If the Patent Office

decides that the first two rows of data in Table3 should be canceled, Applicants will do so. Alternatively, if the Patent Office decides that Table 3 should be amended to include the correct amounts of citric acid in the first two rows of data, Applicants will so amend Table 3. On the other hand, if the Patent Office decides that these remarks on the record are sufficient, Applicants will abide by that decision.

Applicants submit that the application is now in condition for allowance, and early notification of such action is earnestly solicited.

Respectfully submitted,

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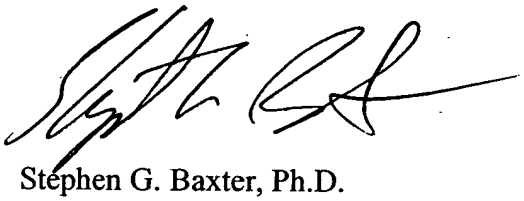

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